Prognosis in Heart Failure and the Value of β-Blockers Are Altered by the Use of Antidepressants and Depend on the Type of Antidepressants Used

Emil Loldrup Fosbøl, MB; Gunnar H. Gislason, MD, PhD; Henrik Enghusen Poulsen, MD, DMSc; Morten Lock Hansen, MD; Fredrik Folke, MD; Tina Ken Schramm, MD; Jonas Bjerring Olesen, MB; Ditte-Marie Bretler, MD; Steen Z. Abildstrøm, MD, PhD; Rikke Sørensen, MD; Anders Hvelplund, MD; Lars Køber, MD, DMSc; Christian Torp-Pedersen, MD, DMSc

Background—Depression worsens the prognosis in patients with cardiac disease, and treatment with antidepressants may improve survival. Guidelines recommend use of selective serotonin reuptake inhibitors (SSRIs), but knowledge of the prognostic effect of different classes of antidepressants is sparse.

Methods and Results—We studied 99 335 patients surviving first hospitalization for heart failure (HF) from 1997 to 2005. Use of HF medication and antidepressants (divided into tricyclic antidepressants [TCA] and SSRI) was determined by prescription claims. Risk of overall and cardiovascular death associated with antidepressants, HF medication, and coadministration of these 2 drug classes was estimated by Cox proportional hazard analyses. Propensity adjusted models were performed as sensitivity analysis. During the study period, there were 53 988 deaths, of which 83.0% were due to cardiovascular causes (median follow-up, 1.9 years; 5, 95% fractiles, 0.04 to 7.06 years). Use of β-blockers was associated with decreased risk of cardiovascular death (hazard ratio [HR], 0.77; 95% CI, 0.75 to 0.79). Antidepressants were prescribed to 19 411 patients, and both TCA and SSRI were associated with increased risk of overall and cardiovascular death (TCA: HR, 1.33; CI, 1.26 to 1.40; and HR, 1.25; CI, 1.17 to 1.32; SSRI: HR, 1.37; CI, 1.34 to 1.40; and HR, 1.34; CI, 1.30 to 1.38, respectively). Coadministration of SSRI and β-blockers was associated with a higher risk of overall and cardiovascular death compared with coadministration of β-blockers and TCA (P for interaction <0.01).

Conclusions—Use of antidepressants in patients with HF was associated with worse prognosis. Coadministration of SSRIs and β-blockers was associated with increased risk of overall death and cardiovascular death compared with coadministration of TCAs and β-blockers. To further clarify this, clinical trials testing the optimal antidepressant strategy in patients with HF are warranted. **(*Circ Heart Fail*. 2009;2:582-590.)**

Key Words: heart failure ■ antidepressants ■ β-blockers ■ cardiovascular mortality ■ mortality ■ pharmacology ■ depression

Heart failure (HF) constitutes a major health issue and often requires lifelong treatment with multiple drugs. Moreover, depression is common in patients with HF, and ≈25% of the patients receive antidepressant medication. This is noteworthy because depression alone is known to worsen the prognosis in HF.[1–11] Various reasons for this observed increased risk of death in depressed patients with HF have been proposed: nonadherence to HF medication,[12,13] smoking and lack of exercise,[14,15] greater catecholamine levels,[16] increased serotonin and platelet activation,[17] and antidepressant toxicity.[18–20] Polypharmaceutical treatment in patients with HF has not been studied systematically, and because depression is associated with a poorer prognosis, spontaneous observations of interactions are unlikely.

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Studies have also suggested that treatment of depression may improve prognosis in patients with HF, but this is currently being tested in randomized trials.[21–23] The importance of antidepressant therapy in a large real-life population of patients with HF has not been investigated. However, 1 clinical trial has suggested a beneficial effect of antidepressant therapy with a selective serotonin reuptake inhibitor (SSRI) agent but only in patients having a substantial reduc-

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From the Department of Cardiology (E.L.F., M.L.H., F.F., T.K.S., J.B.O., D.M.B., R.S., A.H., C.T.P.), Gentofte University Hospital, Hellerup, Denmark; The Heart Centre, Department of Cardiology (G.H.G., L.K.), University Hospital of Copenhagen; Department of Clinical Pharmacology (H.E.P.), University Hospital of Copenhagen, Rigshospitalet, Denmark; Faculty of Health Sciences (H.E.P., L.K., C.T.P.), University of Copenhagen, Copenhagen, Denmark; Cardiovascular Research Unit, Department of Internal Medicine (S.Z.A.), University Hospital Glostrup, Glostrup, Denmark; and National Institute of Public Health (S.Z.A., A.H.), Copenhagen, Denmark.

Correspondence to Emil Loldrup Fosbøl, MB, Department of Cardiology, Gentofte University Hospital, Niels Andersens Vej 65, DK 2900 Hellerup, Denmark. E-mail elf@heart.dk

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tion of depressive symptoms.[24] Because the tricyclic antidepressants (TCAs) show side effects and proarrhythmic effects, caution is recommended by current guidelines, and therefore, SSRIs have become the treatment of choice.[25] However, these guidelines and practices are not clearly substantiated by data but mainly inferred from the current mechanistic knowledge of the drugs and results from few observational studies.[25] Recently, case studies have pointed toward an unfavorable interaction between SSRI and β-blockers,[18,20] and basic pharmacological studies indicate a possible interaction.[26–28] This prompted us to conduct a nationwide cohort study of the effect of antidepressant use in patients with HF and the prognostic importance. In addition, we investigated the adherence to HF medication and interactions between antidepressant and β-blocker treatment.

Methods

Study Design

This study was a historical cohort study in patients with diagnosed HF in Denmark from January 1, 1997, to December 31, 2005. Patients were included in the study at discharge from their first hospital admission with a discharge diagnosis of HF, and follow-up was also started at that date. Outcome measures were death from all causes and cardiovascular disease-specific deaths (*International Classification of Diseases* [ICD] codes I00–I99).

Study Data

All residents in Denmark have a personal and unique personal registration number, which enables linkage of administrative registers on the individual level. Vital status (dead or alive) was obtained from The Danish Civil Registration System, which is updated every second week. Causes of death were obtained from the National Causes of Death Register in which immediate, contributory, and underlying causes are recorded according to the ICD codes. Information on concomitant medication was obtained from the National Prescription Register (the Danish Register of Medicinal Product Statistics) in which all claimed prescriptions in Denmark have been recorded since 1995. The drugs are classified according to the international Anatomic Therapeutical Chemical system. Because of partial reimbursement of drug expenses by the healthcare system, pharmacies in Denmark are required to register all dispensed prescriptions in the National Prescription Register. This ensures a highly accurate register.[29] Comorbidity was obtained from the Danish National Patient Register, which holds information on all admissions to Danish hospitals since 1978.[30] Each admission is registered by 1 primary diagnosis and, if appropriate, 1 or more secondary diagnosis according to the ICD—before 1994, the 8th revision (ICD-8) and since 1994, the 10th revision (ICD-10).

Study Population

The Danish population aged 10 years or more on January 1, 1997, constituted the base population. From 1997 to 2005, all individuals who survived their first hospital admission for HF were included in the study (ICD-10 codes: I11.0, I50, I42, and J81; as primary or secondary diagnosis). First time admission for HF was defined as no previous admission for HF since 1978. The discharge coding diagnosis of HF has been validated in the Danish National Patient Register and has high specificity but low sensitivity.[31]

Medical Treatment: Antidepressants and β-blockers

All prescriptions for β-blockers (Anatomic Therapeutical Chemical code C07) and antidepressants (TCA, Anatomic Therapeutical Chemical code N06AA; SSRI, Anatomic Therapeutical Chemical code N06AB) were obtained from the National Prescription Register. Initiation of β-blocker therapy subsequent to discharge was defined as at least 1 claimed prescription within 90 days after discharge. Baseline use of antidepressants was defined as at least 1 claimed prescription for a TCA or a SSRI within 90 days before or 90 days after discharge. For survival analyses, all treatment intervals according to prescription data were located. The method used to determine the dose and treatment duration has been described previously.[32,33] In brief, for each prescription, number of pills dispensed was divided by the estimated daily dosage to calculate the treatment duration. This method allowed the dosage to change according to refilling patterns of consecutive prescriptions.

Statistical Analysis

Risk of all-cause death and cardiovascular death associated with the use of β-blockers, antidepressants, and a combination of both was estimated by Cox proportional hazard analysis. Use of these drugs was first defined as initiation of treatment in connection with the admission for HF. To assess a more specific relationship between exposure to the drugs and outcome, we also performed Cox proportional hazard analysis with time-dependent variables for exposure. Hence, the patients could change exposure status according to prescription information. Finally, as sensitivity analyses, we performed a stratified propensity-based analysis, ranking patients into tertiles according to propensity of receiving β-blockers within 90 days after discharge by logistic regression analysis conditional on baseline covariates. The Cox models estimating the risk of cardiovascular death were censored for deaths resulting from causes unrelated to the end point of interest (cardiovascular death, ICD code I00-I99). All analyses were adjusted for available covariates (Table 1). The models were also adjusted for nonadherence in taking HF medication. This was done as by Gislason et al[34] by entering time-dependent covariates into the model, allowing the patients to be categorized as nonadherent when experiencing a break of 90 days or more in treatment.

Multivariable analyses of time to first break in therapy with β-blockers, angiotensin-converting enzyme inhibitors and angiotensin-2 receptor antagonists (RASi), and spironolactone of >90 days (representing nonadherence) were performed with Cox proportional hazard models. All models were adjusted for available covariates (Table 1). The assumptions underlying the Cox proportional hazard regression analysis (assumption of linearity and no interaction) were tested and found valid unless otherwise stated. To demonstrate long-term adherence with HF medications according to the use of antidepressant, we plotted the proportion of patients alive who were on treatment on each day.

Unadjusted Kaplan–Meier curves were made according to the baseline use of β-blocker, TCA, and SSRI. For all analyses, a 2-sided P value <0.05 was considered statistically significant. Cox proportional hazard analyses with time-dependent variables were performed using the Stata statistical package, version 10 (Stata Corp, College Station, Tex). All other analyses and data management were performed using SAS, version 9.1 (SAS Institute, Inc, Cary, NC).

Ethics

The Danish Data Protection Agency approved the study (No. 2003-54-1269). In Denmark, historical cohort studies based on data from administrative registers do not require ethical approval.

Results

A total of 99 335 patients survived their first hospitalization for HF during the study period. The median follow-up time was 1.9 years (5, 95% fractiles, 0.04 to 7.06 years). The baseline characteristics are shown in Table 1 according to the type of antidepressant therapy used in connection with the hospitalization for HF. In total, 980 patients received a β-blocker and TCA subsequent to discharge, and 4045 patients received SSRI and a β-blocker. Substantially, more women than men were prescribed with both types of antide-

Table 1. Baseline Characteristics

	TCA	SSRI	No TCA or SSRI	Total
Patients (age, y)	3739 (72.6±11.6)	15672 (75.9±11.0)	80826 (73.9±12.4)	99335 (74.2±12.2)
Male (age, y)	1397 (69.6±11.6)	6544 (73.8±11.1)	43824 (71.2±12.5)	51457 (71.5±12.4)
Female (age, y)	2342 (74.4±11.2)	9128 (77.5±10.6)	36997 (77.1±11.4)	47873 (77.1±11.3)
Year of first hospitalization for HF				
1997–1998	822 (22.0)	2652 (16.9)	17241 (21.3)	20502 (20.6)
1999–2000	843 (22.6)	3302 (21.1)	19059 (23.6)	23006 (23.2)
2001–2002	871 (23.3)	4004 (25.6)	18972 (23.5)	23643 (23.8)
2003–2004	827 (22.1)	3982 (25.4)	17478 (21.6)	22086 (22.2)
2005	376 (10.1)	1732 (11.1)	8076 (10.0)	10098 (10.2)
Discharge diagnosis at first HF hospitalization (ICD-10)				
Hypertensive HF (I11.0)	91 (2.4)	391 (2.5)	2146 (2.7)	2604 (2.6)
Cardiomyopathy (I42)	157 (4.2)	453 (2.9)	4492 (4.6)	5056 (5.1)
Decompensated HF (I50.0 to I50.1)	1110 (29.7)	4757 (30.4)	23971 (29.7)	29562 (29.8)
Unspecified HF (I50.9)	2198 (58.8)	9352 (59.7)	47179 (58.4)	58222 (58.6)
Acute pulmonary edema (J81.9)	183 (4.9)	719 (4.6)	3038 (3.8)	3891 (3.9)
Comorbidity and history				
Myocardial infarction	527 (14.1)	2877 (18.4)	15462 (19.1)	18723 (18.9)
Medically treated diabetes	334 (8.9)	1167 (7.5)	4600 (5.7)	6034 (6.1)
Ischemic heart disease	1076 (28.8)	4891 (31.2)	25137 (31.1)	30848 (31.1)
Cerebrovascular disease	463 (12.4)	3215 (20.5)	7677 (9.5)	11220 (11.3)
Peripheral vascular disease	419 (11.2)	1247 (8.0)	4881 (6.0)	6455 (6.5)
Malignancy	503 (13.5)	1872 (11.9)	8030 (9.9)	10295 (10.4)
Chronic obstructive pulmonary disease	682 (18.2)	3107 (19.8)	12596 (15.6%)	16204 (16.3)
Dementia	6 (0.2)	63 (0.4)	92 (0.1)	160 (0.2)
Renal failure	179 (4.8)	768 (4.1)	3423 (4.2)	4337 (4.4)
Severity group*				
I	1018 (27.2)	4544 (29.0)	24150 (29.9)	29471 (29.7)
II	1483 (39.7)	6142 (39.2)	33182 (41.1)	40450 (40.7)
III	636 (17.0)	2585 (16.5)	13328 (16.5)	16394 (16.5)
IV	602 (16.1)	2401 (15.3)	10166 (12.6)	13020 (13.1)
Medical treatment after discharge				
β-blockers†	980 (26.2)	4045 (25.8)	26719 (33.1)	31515 (31.7)
RASi†	1586 (42.4)	6001 (38.3)	37280 (46.1)	44475 (44.8)
Spironolactone†	812 (21.7)	3280 (20.9)	16862 (20.9)	20751 (20.9)
Statin‡	501 (13.4)	2172 (13.9)	13456 (16.7)	16015 (16.1)
Loop diuretic (furosemide)§	3053 (81.7)	12621 (80.5)	63094 (78.1)	78034 (78.6)

Data are presented as n (mean±SD) or n (%).

*According to average daily dosage of loop diuretic (furosemide) in the first 90 d after discharge (group I, 0 to 39 mg; group II, 40 to 80 mg; group III, 81 to 160 mg; and group IV, >160 mg).

†At least 1 prescription claimed within 90 d from discharge.

‡At least 1 prescription claimed within 180 d from discharge.

§At least 1 prescription claimed between 90 d before admission and 90 d after discharge.

pressants, and patients treated with SSRIs tended to be older than those treated with TCAs.

During the study period, 53 988 patients died (54.4%), of whom 44 554 died of cardiovascular causes. One-year mortality was 25.7% (25 557 patients). Of the 980 patients who received a β-blocker and TCA after discharge, 395 patients died; of the 4045 patients who were prescribed with a β-blocker and SSRI after discharge, 1750 patients died. The Kaplan–Meier curves are shown in Figures 1 and 2 according to baseline initiation of β-blockers and stratified by type of antidepressant. Table 2 shows the results from the Cox proportional hazard analysis demonstrating the association between exposure to HF medication, TCA, and SSRI and the occurrence of death and cardiovascular death (both baseline and time-dependent exposure). The results show a protective effect of β-blockers on both outcomes, whereas use of both types of antidepressants results in an increased risk with a hazard ratio of >1. The SSRIs were associated with a

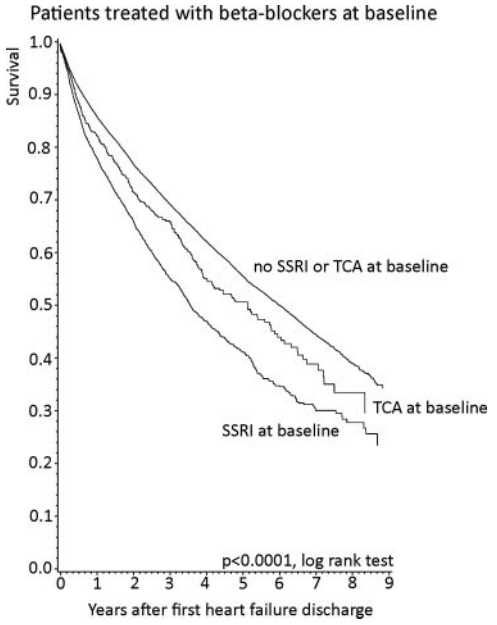

Figure 1. Unadjusted Kaplan–Meier curve according to use of antidepressants, showing patients with heart failure who claimed at least 1 prescription for a β-blocker within 90 days of discharge.

significantly higher risk of cardiovascular death compared with TCAs.

Patients prescribed with TCA did not have an increased risk of nonadherence with any of the HF medications, whereas SSRI was associated with worse adherence to β-blockers and RASi compared with both TCA users and patients taking no antidepressant medication (Table 3). The long-term adherence to HF medication is illustrated by Figure 3A (adherence to β-blockers), Figure 3B (RASi), and Figure 3C (spironolactone) according to the use of antidepressants.

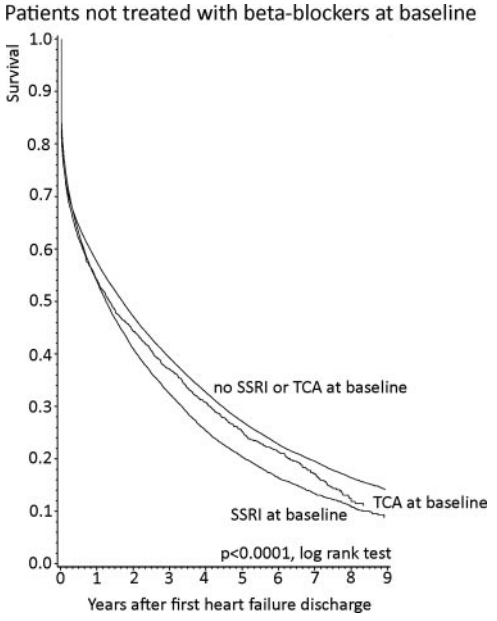

Figure 2. Unadjusted Kaplan–Meier curve according to use of antidepressants. Patients with heart failure who did not claim a prescription for a β-blocker within 90 days of discharge.

We tested for difference in the effect of HF medication (β-blockers, RASi, and spironolactone) according to the type of antidepressant used, and the results showed that there was no difference in the importance of RASi and spironolactone when taking either TCA or SSRI (all P for interaction >0.05). However, there was a difference in the importance of β-blockers according to the type of antidepressant used (P for interaction 0.001 and 0.002 for overall death cardiovascular death, respectively). Hazard ratios for death and cardiovascular death according to treatment with β-blockers and the type of antidepressant are shown in Table 4. The results showed that coadministration of SSRI and β-blockers was associated with increased risk of death and cardiovascular death compared with the use of SSRI alone, TCA alone, and TCA along with β-blockers. Table 5 demonstrates the results derived from the sensitivity analyses in which the model was further adjusted for the patient's probability of receiving β-blockers shortly after discharge (propensity stratified analysis conditional on baseline characteristics). The c statistic was 0.78, indicating good discriminatory power of the model. Results listed in Table 5 support the previous analyses and underline the robustness of the results.

Additional Analyses

We performed sensitivity analyses for exposure to the most frequently used types of β-blockers because case reports on interaction between SSRIs and β-blockers have been reported only on the specific β-blocker, metoprolol. For metoprolol, carvedilol, and bisoprolol, the results were very similar (data not shown) to the results given in Tables 2, 4, and 5, suggesting a class effect.

Discussion

This study has demonstrated that the use of antidepressants as a proxy for depression carries an increased risk of death and cardiovascular death among patients with HF. This increase in risk was further potentiated when SSRIs were coadministered with β-blockers as opposed to coadministration with TCAs and β-blockers. Although both types of antidepressants were associated with increased risk of cardiovascular and all-cause mortality, it seems that the risk associated with the use of SSRIs is greater than that associated with TCAs. This unexpected finding requires confirmation because case reports have reported on possible adverse side effects of combination therapy of only metoprolol and a SSRI.[18,20] We found no similar connection between the use of other mortality-beneficial drugs in HF and antidepressants. In addition, this study documented that the use of SSRIs was associated with increased risk of nonadherence to evidence-based pharmacotherapy in HF, whereas the use of TCAs did not increase risk of nonadherence. Adherence to HF medication has also been proposed to be an important risk factor in HF when depression is present as comorbidity,[12,13,15] and our study suggests that patients taking SSRI have an increased risk of nonadherence to β-blockers and RASi.

Other studies addressing the prognostic importance of depression in patients with cardiac disease have shown that depression is associated with a poor prognosis.[1–6,15] This study confirms that patients with HF have increased risk of

Table 2. Multivariable Adjusted HRs Derived From the Cox Proportional Hazard Analysis: Standard Analysis and Time-Dependent Analysis

	Standard Analysis		Analysis With Exposure Entered in the Model as Time-Dependent Variables	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Death				
BB	0.68 (0.66 to 0.69)	<0.0001	0.83 (0.81 to 0.86)	<0.0001
Sprionolactone	1.13 (1.10 to 1.15)	<0.0001	1.56 (1.52 to to.61)	<0.0001
RASi	0.71 (0.70 to 0.73)	<0.0001	0.72 (0.70 to 0.73)	<0.0001
TCA	1.47 (1.39 to 1.54)	<0.0001	1.33 (1.26 to 1.40)	<0.0001
SSRI	1.51 (1.48 to 1.55)	<0.0001	1.37 (1.34 to 1.40)	<0.0001
Cardiovascular death				
BB	0.80 (0.78 to 0.82)	<0.0001	0.77 (0.75 to 0.78)	<0.0001
Spironolactone	1.03 (1.01 to 1.06)	0.006	1.47 (1.43 to 1.50)	<0.0001
RASi	0.80 (0.78 to 0.81)	<0.0001	0.77 (0.75 to 0.78)	<0.0001
TCA	1.00 (0.95 to 1.05)	0.88	1.25 (1.17 to 1.32)	<0.0001
SSRI	1.09 (1.06 to 1.12)	<0.0001	1.34 (1.30 to 1.38)	<0.0001

The multivariable analysis is adjusted for age, sex, year of HF admission, comorbidity, concomitant pharmacotherapy, and severity of HF (Table 1). BB indicates at least 1 prescription claimed for a β-blocker within 90 days from discharge; RASi, at least 1 prescription claimed within 90 days from discharge of an angiotensin-converting enzyme inhibitors and angiotensin-2 receptor antagonists; TCA, at least 1 prescription claimed for a tricyclic antidepressant between 90 days before admission and 90 days after discharge; SSRI, at least 1 prescription claimed for a selective serotonin reuptake inhibitor between 90 days before admission and 90 days after discharge.

overall and cardiovascular death when treated with antidepressants, which we take as a proxy for depression. Currently, several trials are testing the efficacy of antidepressive intervention on outcome in various groups of patients with cardiac disease.[21–23] Current guidelines on the pharmacological approach to treating depression in patients with cardiac disease state that, although data are lacking, it is recommended that SSRIs are chosen before TCAs.[25] This is, however, not based on data but on the known adverse event profiles or efficacy relation in depression without cardiac disease and the problems with the proarrhythmic risk associated with the TCAs. One study has reported an increase in risk of myocardial infarction associated with the use of TCAs,[35] and it is also known that TCAs prolong the QT interval and increase the risk of sudden cardiac death.[28,36,37] Furthermore, 1 head-to-head study of nortriptyline compared with paroxetine in patients with ischemic heart disease showed that patients discontinued treatment with nortriptyline more often than paroxetine because of cardiovascular adverse events.[38] Another explanation for why we found worse prognosis associated with the use of SSRIs compared with TCAs may also be that patients initiated on TCAs were healthier compared with SSRI users, thus representing a selection bias. Another study has reported decreased cardiovascular risk when treated with SSRIs.[39] On the contrary, Sherwood et al recently reported that antidepressants carry an independent increase in risk irrespective of depression in outpatients with HF, which is in accordance with this study. In addition, only 1 small nonrandomized study has recently investigated the importance of coadministration of β-blockers and antidepressants. The study suggested that patients with end-stage HF and depression who were treated with SSRIs had better survival compared with patients who were treated with TCAs.[40] However, this study was conducted on a large unselected cohort of patients with HF with complete and nationwide data representing a real-life scenario. This discrepancy underlines the fact that more studies are warranted on this subject. Overall, previous studies question the safety of both TCAs and SSRIs for the treatment of depression in patients with HF, but confirmative data on this subject are lacking. An increased risk of adverse outcome in patients treated with SSRI compared with TCA could be explained by increased platelet activation by serotonin or by direct stimulation of the myocardium.[41] Further studies need to assess whether treatment with SSRIs increase the plasma level of serotonin enough to stimulate the myocardium. Because depression is a major comorbidity in HF with a possible survival benefit when treated, it is crucial that the optimal treatment regimen is found; whether or not this should be pharmacological is also a relevant question. We believe that our study questions the

Table 3. Multivariable Cox Proportional Hazard Analysis of Time to First Break in Treatment of >90 Days (Proxy for Nonpersistence) in HF

	β-Blockers, HR (95% CI)	RASi, HR (95% CI)	Spironolactone, HR (95% CI)
No TCA or SSRI	1.0	1.0	1.0
TCA	0.97 (0.88 to 1.06)*	1.04 (0.95 to 1.14)†	1.04 (0.94 to 1.14)‡
SSRI	1.31 (1.07 to 1.19)*	1.16 (1.10 to 1.22)†	1.02 (0.96 to 1.07)‡

*P=0.007 for the difference between the hazard ratios for TCA versus SSRI.
†P=0.04 for the difference between the hazard ratios for TCA versus SSRI.
‡P=0.7 for the difference between the hazard ratios for TCA versus SSRI.

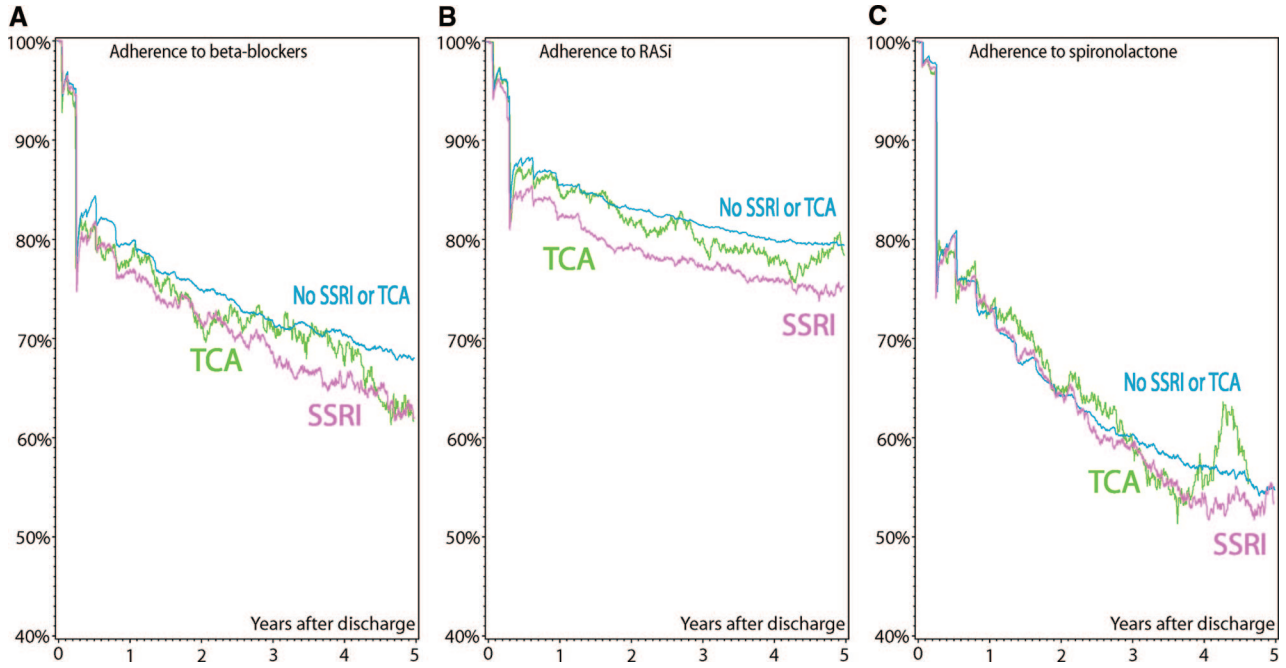

Figure 3. Percentage of patients taking heart failure medication after discharge for heart failure illustrating the long-term adherence to β-blockers (A), RASi (B), and spironolactone (C) according to use of antidepressant medication. TCA indicates tricyclic antidepressants; SSRI, selective serotonin reuptake inhibitors.

use of SSRIs in combination with β-blockers and that a large clinical trial is crucial in analyzing risk and efficacy in the treatment of depression among patients with HF. Furthermore, this results underline the prognostic importance of depression in HF and demonstrate the need for more thorough follow-up of these high-risk patients and the need for expert care.

Currently, the mechanism by which a possible adverse interaction between β-blockers and SSRIs is established is unknown. Several possibilities can be put forward. An interaction based on inhibition of β-blocker metabolism in the liver is a possibility because SSRIs have been shown to inhibit the major pathway of elimination of some β-blockers. However, both types of drugs act on neurotransmitters and nervous transmissions in both the brain and the heart, and possibly in other organs as well. However, these mechanisms are only speculative and not supported by solid data, which can determine the plausibility. The results of this study may possibly be explained by drug metabolism and by drug action. In vitro studies have shown that SSRIs inhibit CYP2D6, which mediates ≈60% of the biotransformation of the β-blocker metoprolol to α-hydroxymetoprolol and *O*-demethylmetoprolol in the human liver. Studies in human liver microsomes suggest that α-hydroxylation of metoprolol

Table 4. Multivariable Adjusted HRs Derived From the Cox Proportional Hazard Analysis: Standard Subgroup Analyses and Time-Dependent Analyses

	Standard Analysis		Analysis With Exposure Entered in the Model as Time-Dependent Variables	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Death				
Treatment with TCA and BB	1.13 (1.02 to 1.25)	0.02	1.46 (1.30 to 1.66)	<0.0001
Treatment with TCA but no BB	1.12 (1.07 to 1.17)	<0.0001	1.45 (1.36 to 1.55)	<0.0001
Treatment with SSRI and BB	1.38 (1.31 to 1.45)	<0.0001	1.47 (1.40 to 1.55)	<0.0001
Treatment with SSRI but no BB	1.16 (1.13 to 1.19)	<0.0001	1.31 (1.30 to 1.35)	<0.0001
Cardiovascular death				
Treatment with TCA and BB	1.10 (0.99 to 1.23)	0.1	1.28 (1.12 to 1.45)	0.001
Treatment with TCA but no BB	1.06 (0.99 to 1.11)	0.06	1.16 (1.08 to 1.24)	<0.0001
Treatment with SSRI and BB	1.31 (1.24 to 1.38)	<0.0001	1.37 (1.30 to 1.44)	<0.0001
Treatment with SSRI but no BB	1.13 (1.10 to 1.17)	<0.0001	1.18 (1.14 to 1.28)	<0.0001

The multivariable analysis is adjusted for age, sex, year of HF admission, comorbidity, concomitant pharmacotherapy, adherence to HF medication, and severity of HF (Table 1). BB indicates β-blockers.

Table 5. Propensity Score Adjusted Analyses: HRs Derived From the Cox Proportional Hazard Analysis—Standard Subgroup Analyses and Time-Dependent Analyses Adjusted for Propensity Score for Receiving β-Blockers After Discharge

	Standard Analysis		Analysis With Exposure Entered in the Model as Time-Dependent Variables	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Death				
Treatment with TCA and BB	1.13 (1.02 to 1.26)	0.02	1.33 (1.18 to 1.51)	<0.0001
Treatment with TCA but no BB	1.05 (0.99 to 1.10)	0.06	1.39 (1.40 to 1.59)	<0.0001
Treatment with SSRI and BB	1.37 (1.29 to 1.45)	<0.0001	1.36 (1.29 to 1.44)	<0.0001
Treatment with SSRI but no BB	1.08 (1.05 to 1.10)	<0.0001	1.26 (1.22 to 1.30)	<0.0001
Cardiovascular death				
Treatment with TCA and BB	1.05 (0.92 to 1.19)	0.6	1.10 (1.05 to 1.15)	0.0006
Treatment with TCA but no BB	1.00 (0.88 to 1.13)	0.7	1.10 (1.02 to 1.19)	0.008
Treatment with SSRI and BB	1.24 (1.16 to 1.33)	<0.0001	1.30 (1.23 to 1.36)	<0.0001
Treatment with SSRI but no BB	1.00 (0.96 to 1.04)	0.6	1.13 (1.09 to 1.17)	<0.0001

The multivariable analysis is adjusted for age, sex, year of HF admission, comorbidity, concomitant pharmacotherapy, adherence to HF medication, and severity of HF (Table 1). BB indicates β-blockers.

occurs almost exclusively, and O-demethylation partially, through CYP2D6.[42] A study on in vivo data indicates that ≈70% of the metabolism of metoprolol depends on CYP2D6.[43] Furthermore, we also know that biotransformation of metoprolol is inhibited by most SSRIs and SSRI metabolites. Of these, fluoxetine, paroxetine, and norfluoxetine are the most potent inhibitors.[44]

Furthermore, another explanation for the observed results may be of opposite etiology: higher plasma levels of serotonin due to a competitive relationship between SSRI and β-blockers in CYP450 enzyme oxidation. Higher levels of serotonin in these patients with HF could pose a detrimental effect on the myocardium as proposed by animal studies and possibly increase risk of fibrosis and valvular disease.[28,41] Furthermore, increased platelet activation by serotonin could also be a mechanism in which prognosis may be affected by higher levels of serotonin in plasma.[17]

It has not been studied whether the in vivo plasma concentrations of metoprolol are increased when paroxetine or fluoxetine are coadministered. Two case reports describing an interaction between metoprolol and an SSRI (fluoxetine and paroxetine) support this.[18,20] Belpaire et al concluded that fluoxetine, norfluoxetine, and paroxetine are potent inhibitors of the in vitro metabolism of metoprolol, suggesting a possible in vivo interaction; fluvoxamine, sertraline, and citalopram are less potent inhibitors. In our study, we grouped all β-blockers as one, but as an additional analysis, we also performed all analyses for metoprolol, carvedilol, and bisoprolol separately to investigate the physiological etiology of the pharmaceutical interaction. The results were similar for all drugs, suggesting a class effect rather than an effect valid only for metoprolol. Hence, the biological evidence is currently sparse, but suggesting a plausible causative relationship.

Strengths and Limitations

This study is based on complete and nationwide data. The data cover the entire population of Denmark independent of race, socioeconomic status, age, or participation in health-insurance programs. Therefore, the risk of selection bias is minimized, and the study notably includes citizens both in and out of the labor market. The Danish healthcare system partially reimburses drug expenses, and all Danish pharmacies are thus required to register all dispensed drug prescriptions, which ensures complete registration. Furthermore, because there is partial patient copayment of drug expenses in Denmark, patients needing higher doses or long-term treatment would have a financial incentive to obtain a prescription from their physician to receive reimbursement. In Denmark, all β-blockers and antidepressants can be purchased only through prescription.

The main limitation is inherited in the observational nature of the study. We have no information about the precise indication for initiation of antidepressant treatment. However, we must assume that an individual prescribed with antidepressant medication has a relevant diagnosis constituting this treatment. Another important limitation is the lack of detailed information about important prognostic factors such as left ventricular ejection fraction, New York Heart Association classification, smoking status, systolic blood pressure, renal function, serum sodium, and lipid levels. We have adjusted the analyses for important comorbidity factors and concomitant pharmacotherapy; however, because this is an observational study, it is important to acknowledge that the effect of unmeasured confounders cannot be completely excluded. Therefore, the results observed in this study could perhaps be explained by differences in patient characteristics and disease severity described by covariates that are unavailable to us. Furthermore, we cannot rule out the possibility that the patients treated with TCAs in connection with their first hospitalization for HF are indication-wise similar to patients treated with SSRIs. However, all applied analyses showed consistent results, and this underlines the robustness of the findings. Because the current guidelines state that a SSRI always should be preferred before a TCA, there is a possi-

bility that patients treated with TCAs have more severe depression or have had depression for longer time than patients treated with SSRIs. Furthermore, TCAs can potentially prolong the QT interval, and therefore, an electrocardiographic control is part of the initiation of treatment with these drugs. This could mean that patients with more severe cardiac disease were less likely to be started on a TCA. However, this difference in initiation of the type of antidepressant cannot explain the observed difference when the patients are coadministrated with β-blockers.

To assess a more accurate estimation of the association between coadministration of the drugs and outcome, we used several different statistical methods. Models with exposure defined at baseline and as time-dependent variables gave more or less the same result, and the propensity stratified analyses underlined this. We ascribe the time-dependent analysis more value because it takes into account the fluctuating use of both antidepressants and β-blockers in time. Notably, risk of cardiovascular death was significantly higher in individuals treated with SSRIs and β-blockers compared with those treated with TCAs and β-blockers. This further strengthens a causative relationship because an increase in risk of all-cause death alone would support a confounding-by-indication theory as explanation.

Conclusions and Implications

This study demonstrated that the use of SSRIs and TCAs in connection with first hospitalization for HF is associated with worse prognosis. The use of SSRIs was associated with a higher increase in risk of overall mortality and cardiovascular death compared with the use of TCAs. Furthermore, our study raises concern on the coadministration of SSRIs and β-blockers in patients with HF. From an ethical point of view, clarification from a randomized trial is warranted. We also found an increased risk of nonadherence to HF medication associated with the use of SSRIs but not with TCAs. However, after adjusting for nonadherence, the overall results were unchanged. Thus, the increased risk associated with SSRI and β-blocker use could not be explained by nonadherence to lifesaving HF medication. Further investigations are needed to clarify the importance of type of antidepressant therapy in patients with HF needing β-blockade.

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Disclosures

None.

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CLINICAL PERSPECTIVE

Depression is common in patients with heart failure (HF), and ≈25% of the patients receive antidepressant medication, which is noteworthy because depression alone is known to worsen the prognosis in HF. Various reasons for this observed increased risk of death in depressed patients with HF have been proposed, including nonadherence to HF medication; smoking and lack of exercise; greater catecholamine levels; increased serotonin and platelet activation; and antidepressant toxicity. In this study, we used Danish administrative registers to investigate the prognostic importance of antidepressant therapy according to the type of antidepressants used among patients diagnosed with HF. Treatment of depression was independently associated with worse prognosis, and selective serotonin reuptake inhibitors increased the risk of death and cardiovascular death more than tricyclic antidepressants. Surprisingly, coadministration of serotonin reuptake inhibitors and β-blockers was associated with a higher risk of death and cardiovascular death compared with coadministration of β-blockers and tricyclic antidepressants. The findings were independent of adherence to HF medication, comorbidity, concomitant pharmacotherapy, and HF severity and challenge the current guidelines. Hence, experimental investigations are needed to clarify the importance of type of antidepressant therapy in patients with HF needing β-blockade.

Prognosis in Heart Failure and the Value of β-Blockers Are Altered by the Use of Antidepressants and Depend on the Type of Antidepressants Used

Emil Loldrup Fosbøl, Gunnar H. Gislason, Henrik Enghusen Poulsen, Morten Lock Hansen, Fredrik Folke, Tina Ken Schramm, Jonas Bjerring Olesen, Ditte-Marie Bretler, Steen Z. Abildstrøm, Rikke Sørensen, Anders Hvelplund, Lars Køber and Christian Torp-Pedersen

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